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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/856,050 | 05/17/2001 | Hidetoshi Uemura | UEMURA 8 | 4088 |

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| EXAMINER | |
|---|---|
| RAMIREZ, DELIA M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/856,050 | UEMURA ET AL. | |
| | Examiner | Art Unit | |
| | Delia M. Ramirez | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,6,13 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,6* is/are allowed.

6)☒ Claim(s) *13 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Application*

Claims 1, 6, 13, 17 are pending.

Applicant's amendment of claims 1, 6,13, 17, and cancellation of claims 20, 27 in a communication filed on 9/14/2004 are acknowledged.

Upon further consideration, the finality of the previous Office Action, mailed on 4/21/2004 is hereby withdrawn due to new ground(s) of rejection not previously introduced.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claim 17 is indefinite in the recitation of "said animal cell is an insect cell" since there is no antecedent basis for an animal cell. It is suggested that the term be amended to recite "said host cell is an insect cell" to be consistent with the preamble. Correction is required.

### *Claim Rejections - 35 USC § 103*

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over the Invitrogen 1997 product catalog in view of Yamashiro et al., Biochimica et Biophysica Acta 1350(1):11-14, 1997. The Invitrogen 1997 catalog teaches the pRSET A, B, C vectors for prokaryotic expression of proteins (page 37), host cells comprising the vectors and pRSET A. B, C vectors comprising a recombinant protein as a positive expression control (page 37, Contents and Storage). These vectors all comprise the nucleotide sequence encoding the enterokinase cleavage site (page 37, Description) which contains the peptide DDDDK (page 12, right column, Description). pRSET A, B, C also contain a polynucleotide sequence encoding a polyhistidine tag (His6). The cloning site in pRSET A, B, C (i.e. MCS) is immediately after the polynucleotide encoding the enterokinase cleavage site, and the polynucleotide encoding the enterokinase cleavage site is immediately after the polynucleotide encoding His6. pRSET A, B, C do not have a polynucleotide encoding an IgG (k) or a trypsin signal peptide. A target protein produced using the pRSET vectors would be a recombinant fusion protein until enterokinase is used to cleave the His6 tag. In addition, the Invitrogen 1997 catalog teaches the pSecTag2 vectors for expression in mammalian cells. psecTag2 vectors comprise a polynucleotide encoding the mouse IgG(k) secretion signal, a cloning site, a polynucleotide encoding the C-terminal c-myc epitope for detection with the anti-myc antibody, and a polynucleotide encoding a His6 tag (page 46, left column, Description). The Invitrogen 1997 product catalog does not teach cloning of a polynucleotide encoding neurosin in the cloning site.

Yamashiro et al. teaches expression of neurosin in COS-1 cells (mammalian cells) by transforming those cells with a mammalian plasmid (vector) encoding a fusion protein containing the signal peptide for human trypsin II, followed by an enterokinase cleavage site and neurosin (page 14, left column, lines 9-24). Upon cleavage with enterokinase, free neurosin was obtained. Yamashiro et al. does not teach the pRSET or pSecTag vectors of the Invitrogen 1997 catalog.

Claim 13 is directed to an expression vector comprising a nucleotide sequence encoding an IgG(k) or a trypsin secretory signal peptide, a nucleotide sequence encoding a polyhistidine tag, a nucleotide sequence encoding a polypeptide comprising amino acids 36-40 of SEQ ID NO: 19 (DDDDK), and a cloning site into which a polynucleotide encoding a target protein is inserted, wherein the target protein is neurosin.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an expression vector wherein said vector comprises a nucleotide sequence encoding an IgG(k) or a trypsin secretory signal peptide, a nucleotide sequence encoding a polyhistidine tag, a nucleotide sequence encoding a polypeptide comprising amino acids 36-40 of SEQ ID NO: 19 (DDDDK; enterokinase cleavage site), and a cloning site into which a polynucleotide encoding neurosin is inserted.

A person of ordinary skill in the art is motivated to modify the pRSET vector such that the IgG(k) secretion signal of the pSecTag vector and the polynucleotide encoding neurosin taught by Yamashiro et al. are added for the benefit of creating an expression vector which allows for secretion of neurosin fused to a purification tag. Furthermore, a person of ordinary skill in the art is motivated to add the pRSET's polynucleotide encoding the enterokinase cleavage site to the pSecTag vector next to the His6 tag for the benefit of being able to cleave the His6 tag from neurosin after purification. In addition, a person of ordinary skill in the art is motivated to place the polynucleotide encoding the His6 tag prior to the cloning site as the His6 tag may affect the folding/activity of the protein of interest depending on whether the His6 tag is at the C or N terminus. The benefits of secreting a recombinant protein are well known in the

art as secretion to the extracellular medium avoids additional steps in the isolation and purification of the desired protein. In addition, Yamashiro et al. teaches secretion of neurosin using the human trypsin II secretion signal. The benefits of adding a purification tags are well known in the art as purification tags would allow for additional flexibility in the purification process and additional purity.

One of ordinary skill in the art has a reasonable expectation of success at modifying the pRSET vector to include a polynucleotide encoding the IgG(k) secretion signal of the pSecTag vector or modify the pSecTag vector such that the His6 tag is placed upstream from the N-terminus of neurosin and an enterokinase cleavage site is placed next to the His6 tag, since the Invitrogen 1997 catalog teaches expression vectors comprising all the required elements, i.e. IgG(k) secretion signal, His6 tag, enterokinase cleavage site, and cloning site. In addition, Yamashiro et al. teaches the expression of neurosin in a mammalian system (COS-1 cells) wherein neurosin is produced as a fusion protein comprising a signal peptide and an enterokinase cleavage site upstream from the N-terminus of neurosin. Furthermore, the molecular biology techniques required to place the required elements in the order recited are well known in the art. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

### *Allowable Subject Matter*

7. Claims 1 and 6 appear to be allowable over the prior art of record.

8. Claim 17 appears to be allowable over the prior art of record but it is rejected as being indefinite for the reasons indicated above.

### *Conclusion*

9. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the

notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

10. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
October 6, 2004

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600